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Soluble compositions of triphenylethylene antiestrogens

Abstract:

Aqueous compositions of nonsteroidal triphenylethylene antiestrogens for pharmaceutical use comprising as a solubility enhancing agent a pharmaceutically acceptable mono- or dicarboxylic acid having 1-5 carbon atoms, wherein the carbon chain may further contain 1-4 hydroxyl, 1-3 oxo, or one or several halogen a substituents, or a corresponding anion thereof, or methanesulfonic acid or its corresponding anion, in molar excess with respect to the triphenylethylene antiestrogen, optionally together with an organic water miscible co-solvent such as polyethylene glycol (PEG), propylene glycol, ethanol or isopropanol.</PTEXT>

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(71) Applicant *(for all designated States except US)*: ORION CORPORATION [FI/FI]; Orionintie 1, FIN–02200 Espoo (FI).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: KIESVAARA, Juha [FI/FI]; Tammikallionpolku A 3, FIN–20660 Littoinen (FI). ÖRN, Gunilla [FI/FI]; Vilkastuksenkatu 7 C 13, FIN–20320 Turku (FI). KANANEN, Mikko [FI/FI]; Kimukuja 6 A 7, FIN–70780 Kuopio (FI). KORTESUO, Pirjo [FI/FI]; Muddaistentie 139, FIN–21600 Parainen (FI). NISKANEN, Heikki [FI/FI]; Vilkastuksenkatu 7 C 13, FIN–20320 Turku (FI). SALMIA, Jukka [FI/FI]; Metsätie 11 as 4, FIN–21620 Kuusisto (FI). AF URSIN, Kaija [FI/FI]; Koltankuja 4, FIN–20750 Turku (FI).

(74) Agent: ORION CORPORATION; Orion Pharma, Industrial Property Rights, P.O. Box 65, FIN–02101 Espoo (FI).

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(57) Abstract

The invention relates to aqueous compositions of nonsteroidal triphenylethylene antiestrogens for pharmaceutical use comprising as a solubility enhancing agent a pharmaceutically acceptable mono– or dicarboxylic acid having 1–5 carbon atoms, wherein the carbon chain may further contain 1–4 hydroxyl, 1–3 oxo, or one or several halogen substituents, or a corresponding anion thereof, or methanesulfonic acid or its corresponding anion, in molar excess with respect to the triphenylethylene antiestrogen, optionally together with an organic water miscible co–solvent such as polyethylene glycol (PEG), propylene glycol, ethanol or isopropanol.

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SOLUBLE COMPOSITIONS OF TRIPHENYLETHYLENE ANTIESTROGENS

Background of the invention

The present invention relates to aqueous solutions of nonsteroidal triphenylethylene antiestrogens for pharmaceutical use and to methods for the preparation thereof.

Toremifene, tamoxifen, 3-hydroxytamoxifen (droloxifene), 4-hydroxytamoxifen, idoxifene, raloxifene, levormeloxifene, centchroman, clomiphene and their pharmaceutically acceptable salts are examples of nonsteroidal triphenylethylene antiestrogens useful in the treatment of estrogen dependent disorders, e.g. in the prevention or treatment of estrogen receptor positive breast cancer. This class of compounds share the triphenylethylene structure and the compounds are generally very poorly soluble to water. There is a need for stable aqueous formulations of nonsteroidal triphenylethylene antiestrogens and their pharmaceutically acceptable salts, which would be suitable for e.g. high concentration parenteral, transdermal or topical formulations. Parenteral formulations of toremifene in the form of an emulsion, liposome or cyclodextrin complex have been described in WO 93/11757. Transdermal formulations of toremifene in DMSO/ethanol/methylcellulose/water have been described in WO 93/19746. Percutaneous hydroalcoholic gel of 4-hydroxytamoxifen has been described in US 4,919,937. However, these prior formulations are cumbersome to prepare, are irritating or do not provide sufficiently high concentration solutions of nonsteroidal triphenylethylene antiestrogens.

Summary of the invention

It has been found that aqueous solutions of nonsteroidal triphenylethylene antiestrogens and their pharmaceutically acceptable salts with high drug concentrations can be prepared by using as a solubility enhancing agent a pharmaceutically acceptable mono- or dicarboxylic acid having 1-5 carbon atoms, wherein the carbon chain may further contain 1-4 hydroxyl, 1-3 oxo, or one or several halogen substituents, or a corresponding anion thereof, or methanesulfonic acid or its corresponding anion, in molar excess with respect to the triphenylethylene antiestrogen. Furthermore, it was found that pH of such formulations can be increased to nearly neutral without precipitation of the triphenylethylene drug if the solubility enhancing agent is used together with an organic water miscible co-

solvent, preferably polyethylene glycol (PEG), propylene glycol, ethanol or isopropanol or a combination thereof.

Detailed description of the invention

The present invention provides an aqueous composition of a nonsteroidal triphenylethylene antiestrogen or a pharmaceutically acceptable salt thereof comprising as a solubility enhancing agent a pharmaceutically acceptable mono- or dicarboxylic acid having 1-5 carbon atoms, wherein the carbon chain may further contain 1-4 hydroxyl, 1-3 oxo, or one or several halogen substituents, or a corresponding anion thereof, or methanesulfonic acid or its corresponding anion, in molar excess with respect to the triphenylethylene antiestrogen.

The present invention also provides an aqueous composition of a nonsteroidal triphenylethylene antiestrogen or a pharmaceutically acceptable salt thereof comprising as a solubility enhancing agent a pharmaceutically acceptable mono- or dicarboxylic acid having 1-5 carbon atoms, wherein the carbon chain may further contain 1-4 hydroxyl, 1-3 oxo, or one or several halogen substituents, or a corresponding anion thereof, or methanesulfonic acid or its corresponding anion, in molar excess with respect to the triphenylethylene antiestrogen together with an organic water miscible co-solvent.

The present invention further provides a method for preparing aqueous composition of a nonsteroidal triphenylethylene antiestrogen or a pharmaceutically acceptable salt thereof comprising contacting a nonsteroidal triphenylethylene antiestrogen or a pharmaceutically acceptable salt thereof with aqueous media and a solubility enhancing agent selected from a group consisting of a pharmaceutically acceptable mono- or dicarboxylic acid having 1-5 carbon atoms, wherein the carbon chain may further contain 1-4 hydroxyl, 1-3 oxo, or one or several halogen substituents, or a corresponding anion thereof, or methanesulfonic acid or its corresponding anion, in molar excess with respect to the triphenylethylene antiestrogen.

The present invention also provides a method for preparing aqueous composition of a nonsteroidal triphenylethylene antiestrogen or a pharmaceutically acceptable salt thereof comprising contacting a nonsteroidal triphenylethylene antiestrogen or a pharmaceutically acceptable salt thereof with aqueous media, an organic water miscible co-solvent and a solubility enhancing agent selected from a group consisting of a pharmaceutically acceptable mono- or dicarboxylic acid having 1-5 carbon atoms, wherein the carbon chain may further contain 1-4 hydroxyl, 1-3

oxo, or one or several halogen substituents, or a corresponding anion thereof, or methanesulfonic acid or its corresponding anion, in molar excess with respect to the triphenylethylene antiestrogen.

The solubility enhancing agent is used in molar excess with respect to the nonsteroidal triphenylethylene antiestrogen. Preferably, the solubility enhancing agent is used in at least about 1.5 fold, more preferably at least about 2 fold, molar excess, e.g. from about 2 to about 100 fold, typically from about 2 to about 10 fold, with respect to the nonsteroidal triphenylethylene antiestrogen.

The carbon chain of the solubility enhancing agent of the invention may be straight or branched, saturated or unsaturated carbon chain.

Suitable solubility enhancing agents having branched carbon chain include citramalic acid and isobutyric acid, and the corresponding anions.

Suitable solubility enhancing agents having straight carbon chain include lactic acid, acetic acid, formic acid, methanesulfonic acid, 3-hydroxybutyric acid, glycolic acid, pyruvic acid, acrylic acid, propionic acid, trifluoroacetic acid, oxalic acid, malonic acid, maleic acid, tartaric acid and glutaric acid or the corresponding anions (lactate, acetate, formate, mesylate, 3-hydroxybutyrate, glycolate, pyruvate, acrylate, propionate, trifluoroacetate, oxalate, malonate, maleate, tartrate and glutarate).

Preferred solubility enhancing agents are mono- or dicarboxylic acids having 1-4 carbon atoms and dicarboxylic acids having 5 carbon atoms, wherein the carbon chain may further contain 1-4 hydroxyl, 1-3 oxo, or one or several, e.g. 1-3, halogen substituents and the corresponding anions. Preferred halogen substituent is fluorine.

More preferred are mono- or dicarboxylic acids having 1-3 carbon atoms and dicarboxylic acids having 5 carbon atoms, wherein the carbon chain may further contain 1-2 hydroxyl or 1 oxo substituent, and the corresponding anions. Such solubility enhancing agents include lactic acid, acetic acid, formic acid, glycolic acid, pyruvic acid, acrylic acid, propionic acid, glutaric acid, oxalic acid or malonic acid, or the corresponding anions.

Still more preferred are monocarboxylic acids having 1-3 carbon atoms and dicarboxylic acids having 5 carbon atoms, wherein the carbon chain may further contain 1-2 hydroxyl substituent, and the corresponding anions. Lactic acid, acetic acid, formic acid, glycolic acid and glutaric acid and the corresponding anions are

particularly preferred. Lactic acid and the corresponding anion (lactate) are most preferred.

Preferably the organic water miscible co-solvent is polyethylene glycol (PEG), propylene glycol, ethanol or isopropanol or a combination thereof. The amount of the organic water miscible co-solvent is usually from about 1 % to about 75 %, preferably from about 5 % to about 50 %, more preferably from about 10 % to about 30 %, by weight of the formulation.

The formulations of the invention can be prepared e.g. by mixing the acid and/or corresponding salt thereof, purified water, and optionally the organic water miscible co-solvent together, and adding thereafter triphenylethylene antiestrogen or salt thereof and agitating the mixture. For example, up to about 50 w-% solutions of a triphenylethylene antiestrogen or salt thereof can be prepared using this procedure. pH of the solution may be adjusted with a water solution of the corresponding acid salt or e.g. sodium hydroxide. Generally, when pH is increased, solubility of a triphenylethylene antiestrogen is decreased. However, by using the organic water miscible co-solvent of the invention solutions having pH only slightly acidic or nearly neutral can be prepared. Highest drug concentrations are obtained when the pH of the solution is below 7, in particular below pH 6. Preferably the pH of the formulation of the invention is between 4 and 7, more preferably between 5 and 7.

Various additives used in the art such as preservatives, e.g. parabens, sodium benzoate or benzoic acid, or various combinations thereof may be used. The solutions of the invention are suitable in the preparation of e.g. high concentration parenteral, transdermal or topical formulations.

The following experiments demonstrate that the water-solubility of a nonsteroidal triphenylethylene antiestrogen or a pharmaceutically acceptable salt thereof can be dramatically improved by using the solubility enhancing agent according to the invention. The experiments also compare the effect of solubility enhancing agents of the invention to other acids such as hydrochloric acid, gluconic acid or citric acid. The experiments also demonstrate that by using an organic water miscible co-solvent according to the invention pH of the solutions can be increased without precipitation of the drug, even if the organic water miscible co-solvents of the invention alone are not able to significantly solubilize the drug.

Experiments

Example 1. Aqueous formulation of toremifene using acetic acid as a solubility enhancing agent (% is calculated by weight of the composition)

Toremifene base	18.4 %
Glacial acetic acid	9.0 %
Purified water	72.6 %

Glacial acetic acid and purified water were mixed, toremifene base was added and dissolved. pH of the solution was about 4.

Example 2. Aqueous formulation of toremifene using lactic acid as a solubility enhancing agent

Toremifene base	52.6 %
Lactic acid (85 %)	24.0 %
Purified water	23.4 %

Lactic acid (85 % water solution) and purified water were mixed, toremifene base was added and dissolved.

Example 3. Aqueous formulation of toremifene using formic acid as a solubility enhancing agent

Toremifene base	8.2 %
Formic acid	1.6 %
Purified water	90.2 %

Formic acid and purified water were mixed, toremifene base was added; toremifene dissolved slowly (in 3 hours).

Example 4. Aqueous formulation of toremifene using methanesulfonic acid as a solubility enhancing agent

Toremifene base	16.7 %
Methanesulfonic acid	66.6 %
Purified water	16.7 %

Toremifene base was dissolved in methanesulfonic acid, then purified water was added. A clear solution was obtained.

Example 5. Aqueous formulation of tamoxifen base using acetic acid as a solubility enhancing agent

Tamoxifen base	44.2 %
Glacial acetic acid	27.9 %
Purified water	27.9 %

Glacial acetic acid and purified water were mixed, tamoxifen base was added and dissolved.

Example 6. Aqueous formulation of tamoxifen base using lactic acid as a solubility enhancing agent

Tamoxifen base	44.0 %
Lactic acid (85 %)	28.0 %
Purified water	28.0 %

Lactic acid (85 % water solution) and purified water were mixed, tamoxifen base was added and dissolved.

Example 7. Aqueous formulation of tamoxifen base using formic acid as a solubility enhancing agent

Tamoxifen base	5.0 %
Formic acid	10.4 %
Purified water	84.6 %

Formic acid and purified water were mixed, tamoxifen base was added and dissolved.

Example 8. Aqueous formulation of tamoxifen base using methanesulfonic acid as a solubility enhancing agent

Tamoxifen base	16.7 %
Methanesulfonic acid	66.6 %
Purified water	16.7 %

Tamoxifen base and methanesulfonic acid were mixed, then purified water was added. A clear solution was obtained.

Example 9. Aqueous formulation of toremifene using lactic acid/lactate as a solubility enhancing agent, pH 5

Toremifene base	3.7 %
Lactic acid (85 %)	1.7 %
Sodium lactate (50 %)	4.4 %
Purified water	90.2 %

Lactic acid and purified water were mixed, toremifene base was added and dissolved. pH was adjusted to about 5 by sodium lactate (50 % water solution).

Example 10. Aqueous formulation of toremifene using lactic acid as a solubility enhancing agent, pH 5

Toremifene base	36.3 %
Lactic acid (85 %)	18.2 %
Sodium hydroxide 2 M	27.3 %
Purified water	18.2 %

Lactic acid and purified water were mixed, toremifene base was added and dissolved. pH was adjusted to about 5 with 2 M sodium hydroxide.

Example 11 (Reference).

Toremifene base	9.1 %
Hydrochlorid acid 1 N	31.8 %
Purified water	59.1 %

Hydrochloric acid and purified water were mixed, toremifene base was added. Toremifene was not dissolved.

Example 12 (Reference).

Toremifene base	1.0 %
Gluconic acid (30 %)	10.6 %
Ethanol (96 %)	88.3 %

Toremifene base and 30 % water solution of gluconic acid were mixed together and ethanol was gradually added. Toremifene was not dissolved.

Example 13. Aqueous formulation of toremifene using lactic acid /lactate and ethanol, pH about 6

Toremifene base	13.6 %
Lactic acid (85 %)	6.8 %
Purified water	13.6 %
Sodium lactate (50 %)	52.4 %
Ethanol (96 %)	13.6 %

Toremifene base was dissolved to the solution of lactic acid and purified water. Ethanol was added and pH was increased by adding sodium lactate. The formulation above was a clear solution, pH about 6.

Example 14. Aqueous formulation of toremifene using lactic acid /sodium hydroxide and ethanol, pH about 6

Toremifene base	36.60 %
Lactic acid (85 %)	18.35 %
Purified water	18.35 %
Sodium hydroxide (10 M)	8.35 %
Ethanol (96 %)	18.35 %

Toremifene base was dissolved to the solution of lactic acid and purified water. Ethanol was added and pH was increased by adding sodium hydroxide. The formulation above was a clear solution, pH about 6.

Example 15. Aqueous formulation of toremifene using lactic acid / sodium hydroxide and PEG 400A

Toremifene base	27.5 %
Lactic acid (85 %)	13.75 %
Purified water	27.5 %
Sodium hydroxide (10 M)	3.75 %
PEG 400A	27.5 %

Toremifene base was dissolved to the solution of lactic acid and purified water. PEG 400A was added and pH was increased by adding sodium hydroxide. The formulation above was a clear solution, pH about 6.

Example 16. Aqueous formulation of toremifene using lactic acid /lactate and isopropanol

Toremifene base	17.7 %
Lactic acid (85 %)	9.3 %
Purified water	18.5 %
Sodium lactate (50 %)	36.0 %
Isopropanol	18.5 %

Toremifene base was dissolved to the solution of lactic acid and purified water. Isopropanol was added and pH was increased by adding sodium lactate. The formulation above was a clear solution, pH about 5.

Example 17. Aqueous formulation of tamoxifen using lactic acid /lactate and ethanol

Tamoxifen base	11.1 %
Lactic acid (85 %)	5.5 %
Purified water	11.1 %
Sodium lactate (50 %)	61.1 %
Ethanol (96 %)	11.2 %

Tamoxifen base was dissolved to the solution of lactic acid and purified water. Ethanol was added and pH was increased by adding sodium lactate. The formulation above was a clear solution, pH about 6.

Example 18. Aqueous formulation of tamoxifen using lactic acid /sodium hydroxide and ethanol

Tamoxifen base	36.5 %
Lactic acid (85 %)	18.3 %
Purified water	18.3 %
Sodium hydroxide (10 M)	8.6 %
Ethanol (96 %)	18.3 %

Tamoxifen base was dissolved to the solution of lactic acid and purified water. Ethanol was added and pH was increased by adding sodium hydroxide. The formulation above was a clear solution, pH about 6.

Example 19. Aqueous formulation of tamoxifen using lactic acid /lactate and PEG 400A

Tamoxifen base	22.2 %
Lactic acid (85 %)	11.1 %
Purified water	22.3 %
Sodium lactate (50 %)	22.2 %
PEG 400A	22.2 %

Tamoxifen base was dissolved to the solution of lactic acid and purified water. PEG 400A was added and pH was increased by adding sodium lactate. The formulation above was a clear solution, pH about 5.

Example 20. Aqueous formulation of tamoxifen using lactic acid /lactate and isopropanol

Tamoxifen base	22.2 %
Lactic acid (85 %)	11.1 %
Purified water	22.3 %

Sodium lactate (50 %)	22.2 %
Isopropanol	22.2 %

Tamoxifen base was dissolved to the solution of lactic acid and purified water. Isopropanol was added and pH was increased by adding sodium lactate. The formulation above was a clear solution, pH about 5.

Example 21. Aqueous formulation of toremifene citrate using lactate, PEG 300 and ethanol

Toremifene citrate	15 %
Purified water	20 %
Sodium lactate (50 %)	40 %
PEG 300	15 %
Ethanol (96 %)	10 %

Toremifene citrate was added to the mixture of all the other components. The formulation above was a clear solution, pH about 5.

Example 22. Aqueous formulation of toremifene using lactic acid/sodium hydroxide, PEG 300 and ethanol, pH about 6.

Toremifene base	28.10 %
Purified water	14.05 %
Lactic acid (85 %)	11.1 %
PEG 300	29.20 %
Ethanol (96 %)	14.05 %
Sodium hydroxide (10 M)	0.55 %

Toremifene base was dissolved to the solution of lactic acid and purified water. PEG 400A and ethanol was added and pH was increased by adding sodium hydroxide. The formulation above was a clear solution, pH about 6.

Example 23. Aqueous formulation of toremifene using acetic acid and ethanol

Toremifene base	17.5 %
Acetic acid	8.7 %
Ethanol (96 %)	73.8 %

Glacial acetic acid and ethanol were mixed, toremifene base was added and dissolved.

Example 24. Aqueous formulation of toremifene using acetic acid/sodium hydroxide and ethanol

Toremifene base	14.6 %
Acetic acid	7.3 %
Ethanol (96 %)	29.4 %
Purified water	43.9 %
Sodium hydroxide (10 M)	4.8 %

Toremifene base was dissolved to the solution of acetic acid and purified water. Ethanol was added and pH was increased by adding sodium hydroxide. The formulation above was a clear solution, pH about 6.

Example 25. Aqueous formulation of toremifene using lactic acid/lactate, propylene glycol and ethanol

Toremifene base	13.3 %
Purified water	13.3 %
Lactic acid (85 %)	6.7 %
Sodium lactate (50 %)	53.3 %
Propylene glycol	6.7 %
Ethanol (96 %)	6.7 %

Toremifene base was dissolved to the solution of lactic acid and purified water. Ethanol and propylene glycol were added and pH was increased by adding sodium lactate. The formulation above was a clear solution, pH about 6.

Example 26. Aqueous formulation of toremifene using 20 % water solution of glycolic acid/sodium hydroxide and ethanol.

Toremifene base	8.3 %
Glycolic acid (20 %)	41.5 %
Ethanol (96 %)	42.1 %
Sodium hydroxide (10 M)	8.1 %

Toremifene base was dissolved to the 20 % water solution of glycolic acid. Ethanol was added and pH was increased by adding sodium hydroxide. The formulation above was a clear solution, pH about 5.

Example 27. Aqueous formulation of toremifene using 30 % water solution of pyruvic acid/sodium hydroxide and ethanol.

Toremifene base	7.6 %
Pyruvic acid (30 %)	41.1 %
Ethanol (96 %)	38.6 %
Sodium hydroxide (10 M)	12.7 %

Toremifene base was dissolved to the 30 % water solution of pyruvic acid. Ethanol was added and pH was increased by adding sodium hydroxide. The formulation above was a clear solution, pH about 5.

Example 28. Aqueous formulation of toremifene using 20 % water solution of acrylic acid/sodium hydroxide and ethanol.

Toremifene base	8.2 %
Acrylic acid (20 %)	40.4 %
Ethanol (96 %)	42.8 %
Sodium hydroxide (10 M)	8.6 %

Toremifene base was dissolved to the 20 % water solution of acrylic acid. Ethanol was added and pH was increased by adding sodium hydroxide. The formulation above was a clear solution, pH about 5.

Example 29. Aqueous formulation of toremifene using 23 % water solution of propionic acid/sodium hydroxide and ethanol.

Toremifene base	8.1 %
Propionic acid (20 %)	41.9 %
Ethanol (96 %)	41.0 %
Sodium hydroxide (10 M)	8.9 %

It was made a 20 % mixture of propionic acid anhydride in water. The mixture was allowed to stand for four days at room temperature. After four days it was assumed that all propionic acid anhydride had reacted with water to make about 23 % water solution of propionic acid. Toremifene base was dissolved to this 23 % water solution of propionic acid. Ethanol was added and pH was increased by adding sodium hydroxide. The formulation above was a clear solution, pH about 5.

Example 30. Aqueous formulation of toremifene using trifluoroacetic acid/sodium hydroxide and ethanol.

Toremifene base	5.2 %
Trifluoroacetic acid	26.3 %
Purified water	17.7 %

Ethanol (96 %)	26.2 %
Sodium hydroxide (10 M)	24.6 %

Toremifene base was dissolved to trifluoroacetic acid. When water was added, the mixture became cloudy. When ethanol was added, the mixture became clear again. pH was increased by adding sodium hydroxide. The formulation above was a clear solution, pH about 2. It should be possible to raise pH to a more neutral value, because trifluoroacetic is already almost totally neutralised at pH 2.

Example 31. Aqueous formulation of toremifene using 10 % water solution of oxalic acid dihydrate and ethanol.

Toremifene base	2.4 %
Oxalic acid dihydrate (10 %)	61.0 %
Ethanol (96 %)	36.6 %

Toremifene base was mixed with 10 % water solution of oxalic acid dihydrate. When ethanol was added, a clear solution was obtained.

Example 32. Aqueous formulation of toremifene using 40 % water solution of malonic acid/sodium hydroxide and ethanol.

Toremifene base	4.4 %
Malonic acid (40 %)	44.5 %
Ethanol (96 %)	22.9 %
Sodium hydroxide (10 M)	28.2 %

Toremifene base was dissolved to the 40 % water solution of malonic acid. Ethanol was added and pH was increased by adding sodium hydroxide. The formulation above was a clear solution, pH about 6.

Example 33. Aqueous formulation of toremifene using 30 % water solution of maleic acid and ethanol.

Toremifene base	8.8 %
Maleic acid (30 %)	44.7 %
Ethanol (96 %)	46.5 %

Toremifene base was mixed with 30 % water solution of maleic acid. When ethanol was added, a clear solution was obtained.

Example 34. Aqueous formulation of toremifene using 30 % water solution of tartaric acid and ethanol.

Toremifene base	9.1 %
Tartaric acid (30 %)	45.4 %
Ethanol (96 %)	45.5 %

Toremifene base was mixed with 30 % water solution of tartaric acid. When ethanol was added, a clear solution was obtained.

Example 35. Aqueous formulation of toremifene using 30 % water solution of glutaric acid/sodium hydroxide and ethanol.

Toremifene base	7.2 %
Glutaric acid (30 %)	40.1 %
Ethanol (96 %)	37.0 %
Sodium hydroxide (10 M)	15.7 %

Toremifene base was dissolved to the 30 % water solution of glutaric acid. Ethanol was added and pH was increased by adding sodium hydroxide. The formulation above was a clear solution, pH about 6.

Example 36. Aqueous formulation of toremifene using 25 % water solution of 3-hydroxybutyric acid/sodium hydroxide and ethanol.

Toremifene base	2.9 %
3-hydroxybutyric acid (25 %)	57.3 %
Ethanol (96 %)	28.9 %
Sodium hydroxide (10 M)	10.9 %

It was made a 30 % solution of 3-hydroxybutyric acid sodium salt in water. The solution was made acidic with hydrochloric acid (pH about 1). Toremifene base and this 25 % water solution of 3-hydroxybutyric acid were mixed together. When ethanol was added, toremifene dissolved. pH was increased by adding sodium hydroxide. The formulation above was a clear solution, pH about 6.

Example 37 (Reference).

Toremifene base	1.0 %
Citric acid (30 %)	10.3 %
Ethanol (96 %)	88.7 %

Toremifene base and 30 % water solution of citric acid were mixed together and ethanol was added gradually. Toremifene was not dissolved.

Example 38 (Reference).

Toremifene citrate	1.0 %
PEG 300	99.0 %

Toremifene citrate was not dissolved to the PEG 300 solution.

Example 39 (Reference).

Solubility of toremifene citrate in ethanol is about 3 mg/ml.

Example 40 (Reference).

Solubility of toremifene citrate in 0.1 M HCl is about 0.03 mg/ml.

CLAIMS

1. Aqueous composition of a nonsteroidal triphenylethylene antiestrogen or a pharmaceutically acceptable salt thereof comprising as a solubility enhancing agent a pharmaceutically acceptable mono- or dicarboxylic acid having 1-5 carbon atoms, wherein the carbon chain may further contain 1-4 hydroxyl, 1-3 oxo, or one or several halogen substituents, or a corresponding anion thereof, or methanesulfonic acid or its corresponding anion, in molar excess with respect to the triphenylethylene antiestrogen.

2. Aqueous composition of claim 1 comprising together with the solubility enhancing agent an organic water miscible co-solvent.

3. Aqueous composition of claim 2 wherein the co-solvent is polyethylene glycol (PEG), propylene glycol, ethanol or isopropanol.

4. Aqueous composition according to any of claims 1 to 3 wherein the solubility enhancing agent is used in at least about 1.5 fold, preferably at least about 2 fold, molar excess with respect to the nonsteroidal triphenylethylene antiestrogen.

5. Aqueous composition according to any of claims 1-4 having pH value between 4 and 7.

6. Aqueous composition according to any of claims 1-5 wherein the nonsteroidal triphenylethylene antiestrogen is toremifene, tamoxifen, droloxifene, 4-hydroxy-tamoxifen, idoxifene, raloxifene, levormeloxifene, centchroman, clomiphene or a pharmaceutically acceptable salt thereof.

7. A method for preparing aqueous composition of a nonsteroidal triphenylethylene antiestrogen or a pharmaceutically acceptable salt thereof comprising contacting a nonsteroidal triphenylethylene antiestrogen or a pharmaceutically acceptable salt thereof with aqueous media and a solubility enhancing agent selected from a group consisting of a pharmaceutically acceptable mono- or dicarboxylic acid having 1-5 carbon atoms, wherein the carbon chain may further contain 1-4 hydroxyl, 1-3 oxo, or one or several halogen substituents, or a corresponding anion thereof, or methanesulfonic acid or its corresponding anion, in molar excess with respect to the triphenylethylene antiestrogen.

8. A method for preparing aqueous composition of a nonsteroidal triphenylethylene antiestrogen or a pharmaceutically acceptable salt thereof comprising contacting a nonsteroidal triphenylethylene antiestrogen or a pharmaceutically acceptable salt thereof with aqueous media, an organic water miscible co-solvent and a solubility enhancing agent selected from a group consisting of a pharmaceutically acceptable mono- or dicarboxylic acid having 1-5 carbon atoms, wherein the carbon chain may further contain 1-4 hydroxyl, 1-3 oxo, or one or several halogen substituents, or a corresponding anion thereof, or

methanesulfonic acid or its corresponding anion, in molar excess with respect to the triphenylethylene antiestrogen.

9. A method of claim 8 wherein wherein the co-solvent is polyethylene glycol (PEG), propylene glycol, ethanol or isopropanol.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 99/01046

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 47/12, A61K 47/20, A61K 31/138
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9924032 A1 (NOVO NORDISK A/S), 20 May 1999 (20.05.99), page 7, line 30 - line 33; page 7, line 4 - line 21; the examples	1-9
X	WO 9416733 A1 (CHIESIFARMACEUTICI S.P.A.), 4 August 1994 (04.08.94), claims 1-5, 8	1-9
X	EP 0826682 A1 (ELI LILLY AND COMPANY), 4 March 1998 (04.03.98), page 5, line 5 - line 19	1-9
X	EP 0839533 A1 (ELI LILLY AND COMPANY), 6 May 1998 (06.05.98), page 5, line 34 - line 55	1-9

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the International Searching Authority
European Patent Office P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel(+31-70)340-2040. Tx 31 651 epo nl.
Fax(+31-70)340-3016

Authorized officer
GERD STRANDELL/EÖ
Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 99/01046

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 9204310 A1 (UNIVERSITY OF GEORGIA RESEARCH FOUNDATION, INC.), 19 March 1992 (19.03.92), claims 11-14; page 24, line 26 - line 33 --- --------	1-9

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02/12/99

International application No.
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Information on patent family members

02/12/99

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PCT/FI 99/01046

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